

**English, P.B., N. Gravitz, R.R. Neutra, D. Siegel and D. Smith (1985). Health effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin and related compounds, California Department of Health Services.**

## EXECUTIVE SUMMARY

Polychlorinated dibenzo-p-dioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs) are two very similar classes of compounds. The basic chemical structures of these two classes are shown in Figure 1.0-1. Each compound consists of two connected benzene rings, with a variable number of chlorines attached. PCDDs and PCDFs are classified into homologue groups depending on the number of chlorines attached to the rings. These homologues are designated Mono- through Octa-CDD/CDF, for one through eight chlorines. Each homologue group is further subdivided into isomers, which are distinguished by the specific placement of the chlorines on the ring positions (numbered 1 through 9 in Figure 1.0-1).

Neither PCDDs nor PCDFs have been produced for commercial use. However, isomers of both classes have been found as contaminants in other commercially used chemicals. In addition, PCDDs and PCDFs are found as combustion products of chlorinated hydrocarbons and even of normal municipal waste.

A number of the PCDD and PCDF isomers have been found to be highly toxic and therefore are of concern even at very low environmental concentrations. Many of the toxic effects of these compounds are associated with specific placement of the chlorines. 2,3,7,8-TetraCDD (TCDD) is probably the most toxic of the isomers (Figure 1.0-2), and other more highly chlorinated PCDDs and PCDFs with chlorine placement at the 2,3,7 and 8 positions appear to be more toxic than when one or more of these positions are not chlorinated. For this reason, this report only considers the tetrachlorinated through octachlorinated PCDDs and PCDFs and examines the toxicity of 2,3,7,8-TCDD in the most detail since this compound has been the most thoroughly investigated.

2,3,7,8-TCDD and other PCDDs and PCDFs have a high acute (lethal toxicity and can produce a number of adverse effects when administered acutely, subchronically, or chronically to laboratory animals. These effects include death, severe weight loss, liver necrosis and hypertrophy, induction of enzyme activities, skin lesions, immunosuppression reproductive toxicity, and teratogenicity. Acute exposure of humans to PCDDs has caused chloracne, a skin lesion which resembles mild to very severe acne, and which often lasts many years after exposure. Acute and chronic human exposure has also been implicated in producing signs of liver toxicity.

The carcinogenic potential of 2,3,7,8-TCDD has been examined in a number of animal bioassays. Two independent studies gave clear evidence that 2,3,7,8-TCDD can induce a carcinogenic response. Significant increases in the incidences of respiratory tract tumors and of hepatocellular hyperplastic nodules/carcinomas were observed in treated rats from a two year feeding study reported by Kociba et al. (1978). In the two year gavage study with rats and mice conducted by NTP (1982), a number of tumor types were found at higher incidences in treated animals. These tumors included hepatocellular neoplastic nodules/carcinomas in rats and

hepatocellular adenomas/carcinomas in mice. Therefore, the staff of DHS agrees with IARC (1982) that there is sufficient evidence to indicate 2,3,7,8-TCDD is carcinogenic in animals.

Epidemiologic studies have given equivocal results. No studies have been performed on groups of people with pure PCDD or PCDF exposure. Case/control studies in Sweden have shown elevated risks for soft-tissue sarcomas among people working with TCDD-contaminated herbicides. Results of US occupational studies also indicate an apparently greater than expected number of soft-tissue sarcomas, but this requires more investigation. Other findings are contradictory, and few results reach statistical significance. Interpreting these studies is complicated by their small sample sizes and their lack of quantitative exposure estimates. Therefore, DHS agrees with the approach of EPA to use results of animal studies for risk assessment, and recommends that 2,3,7,8-TCDD be considered a potential human carcinogen.

The Air Resources Board asked DHS to investigate the health effects of 2,3,7,8-TCDD and other PCDDs and PCDFs with 4,5,6, and 7 chlorines. HexaCDDs are the only other PCDD or PCDF that have been examined for carcinogenicity. A mixture of two 2,3,7,8-HexaCDD isomers was tested by NTP (1980). Increased incidences of liver tumors or neoplastic nodules were found in treated rats and mice. Although there has been some controversy over the magnitude of the response in female rats, three independent pathological evaluations have found a significant increase in the incidence of hepatocellular carcinomas and/or neoplastic nodules. DHS has concluded that the HexaCDDs used in the animal studies should be considered potential human carcinogens. In addition, because of structure-activity considerations and the lack of chronic exposure studies on penta and heptaCDD and CDF isomers, DHS has concluded that these isomers must also be considered potential human carcinogens.

Although octachlorinated CDD and CDF were not included in ARBs request, they are usually reported among total PCDDs and PCDFs. DHS has decided that for the purposes of this document, these two compounds will be considered noncarcinogenic. This is based on the fact that in the small number of toxicology studies on these compounds, they are consistently much less potent than many of the other isomers. However, by following the same logic used to conclude that the other untested isomers are potential carcinogens, these two compounds could also be considered to be carcinogenic.

Threshold considerations have been examined with respect to the adverse effects produced by PCDDs and PCDFs, with particular attention to the carcinogenic effect. The mechanism of action for several of the toxic effects induced by the PCDDs and PCDFs apparently includes binding of the compound to a specific receptor protein found in the cytosol of cells. It is not known whether the carcinogenic effect of 2,3,7,8-TCDD is through this type of mechanism. 2,3,7,8-TCDD has been shown to act as a promoter of carcinogenesis and this may occur through a mechanisms involving binding to the receptor protein or through some other mechanism. In either case the mechanism of action may have a threshold dose level, below which no effect will occur.

Several studies suggest that 2,3,7,8-TCDD does not interact directly with DNA and therefore should produce its carcinogenic effect through an indirect means that is likely to have a threshold dose level. Other studies, however, suggest that 2,3,7,8-TCDD does cause a direct genotoxic

effect. In this case, the mechanisms of action is believed not to have a threshold dose level. In doing a risk assessment on PCDDs and PCDFs, DHS believes that a conservative approach should be taken when there is uncertainty about the mechanisms of action. For this risk assessment, the conservative approach is to base the assessment on the no-threshold approach which was used by EPA (1984).

To extrapolate the carcinogenic risks in human populations from exposure to TCDD and HexaCDD, DHS has used the data from animal bioassays that showed the most sensitive response. Figure 1.0-3 (TCDD) and 1.0-4 (HexaCDD) are plots of the dose-response curves using five dose extrapolation models: multistage, probit, logit, Weibull, and gamma multi-hit. The various models depicted provide low dose estimates of the 95% upper confidence limit of human excess cancer risk from a lifetime of exposure. The staff of DHS prefers the multistage model for low-dose extrapolation. The multistage model is consistent with a widely-held theory of carcinogenicity and generally given health conservative estimates. Therefore, as EPA has done, DHS has used the multistage model to estimate risks of TCDD and HexaCDD exposure, extrapolated to low dose levels.

Using the multistage model for TCDD exposure, the maximum likelihood estimate of lifetime excess cancers is 240 per million population for continuous exposure at an airborne concentration of  $10^{-2}$  ng/m<sup>3</sup>, with a 95% upper confidence limit of 380. For HexaCDD, the maximum likelihood estimate of lifetime excess cancers is 6 per million population from exposure to  $10^{-2}$  ng/m<sup>3</sup>, with a 95% upper confidence limit of 10. These risks reflect the theoretical number of cases which would accumulate over the 70 year lifetime of one million people from continuous daily exposure to air containing 0.01 billionth of a gram of chemical per cubic meter.

DHS recognizes that PCDDs and PCDFs are probably not universally distributed in the ambient air of California. Their main source is thought to be emissions from combustion processes, such as municipal solid waste incinerators. The ARB has projected possible levels of tetra- through Octa - CDDs and CDFs in the air of the Los Angeles Basin, if several solid waste incinerators currently under consideration were to begin operating. The resulting estimated range:

|       | <u>High Estimate</u>                   | <u>Low Estimate</u>                     |
|-------|--|---|
| PCDDs | $1.2 \times 10^{-2}$ ng/m <sup>3</sup> | $0.07 \times 10^{-2}$ ng/m <sup>3</sup> |
| PCDFs | $2.6 \times 10^{-2}$ ng/m <sup>3</sup> | $0.16 \times 10^{-2}$ ng/m <sup>3</sup> |

Total PCDD/PCDF in air from sources such as incinerators is composed of a mixture of PCDD and PCDF homologues and isomers, most of which have never been tested for carcinogenicity. Furthermore, the specific chemicals in this mixture are difficult to separate analytically, and the concentrations of each isomer may vary depending upon the emission source.

Therefore, in order to estimate a range of risks that might result from such ambient air mixtures, DHS has used three scenarios. Each scenario uses the low dose extrapolation for 2,3,7,8 isomer TCDD and HexaCDD described above, but the scenarios make different assumptions about (1) the concentrations of the various PCDD and PCDF isomers in the total mixture, and (2) the

carcinogenic potencies for the majority of PCDDs and PCDFs that have not been tested. The product of these assumptions is an estimated “TCDD equivalent concentration,” that is, the amount of the total mixture that is considered to be as carcinogenic as 2,3,7,8-TCDD.

For the high ambient concentrations given above, the estimated 95% upper confidence limits of excess lifetime cancers from total PCDD/PCDF exposure span 8 to 1400 cancers per million population, depending on the assumptions. For the low ambient concentrations, the 95% upper confidence limits span <1 to 87 cancers per million population, again, depending on the assumptions used.

The lifetime excess risks of cancer must be viewed in the context of the overall probability of developing cancer, which is on the order of 250,000 cases per million population over a lifetime.

Longstreth and Hushon (1983) developed an “acceptable daily intake” (ADI) level for 2,3,7,8-TCDD of 1 picogram per kilogram body weight per day based upon the lowest observed effect levels reported in the literature. These effects were reproductive toxicity in monkeys and immunotoxicity in guinea pigs that occurred at dose levels somewhat above 1 nanogram per kilogram body weight per day. Therefore, there is a safety factor of over 1000 incorporated into Longstreth and Hushon’s proposed ADI. The airborne concentration necessary to give an exposure equal to this ADI is approximately  $0.33 \times 10^{-2}$  ng of 2,3,7,8-TCDD/m<sup>3</sup>. The assumption used above to derive the cancer risk estimates from total ambient PCDDs and PCDFs give estimates of the TCDD equivalent concentration that is near or below the Longstreth and Hushon ADI with its 1000 fold safety factor.

Therefore, the staff of DHS has concluded that toxic effects of PCDDs and PCDFs other than cancer are not expected to occur at predicted ambient levels, and the carcinogenic effect is the appropriate basis for the risk assessment on these compounds.